ST. MICHAEL'S
UNITY HEALTH TORONTO

Cardiology for the Practitioner
Saturday, April 12, 2025
VIRTUAL

Evidence and guideline-recommended management of Heart failure with reduced ejection fraction and cardiomyopathy

Gordon Moe, M.D., FRCP(C), FAHA, FHFSA, FACC

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Presenter Disclosure

Dr. Gordon Moe

Evidence and guideline-recommended management of HFrEF and cardiomyopathy

Relationships with financial sponsors:

- **Grants/Research Support:** BridgeBio Pharma, BMS, Pfizer, Novartis
- **Speakers Bureau/Honoraria:** CHRC
- **Consulting Fees:** BMS, Pfizer, Novartis
- **Patents:** N/A
- **Other:** N/A

OBJECTIVES

1. Discuss the management of heart failure with reduced ejection fraction (HFrEF) including treatments with **contemporary** information
2. Review cardiomyopathy: focus on the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) with **new** information

Case

68-year-old male

- STEMI one month ago, treated with primary PCI to LAD
- Mild congestion in hospital, cleared, discharged on ACEi, β-blocker, ASA and a statin.
- Echo prior to discharge: LVEF 36%, anterior wall hypokinesis
- Seen in clinic 4 weeks after discharge
- Dyspneic, BP 91/65 mmHg, HR 78 bpm, congested
- Lab: Na 132, K 3.8, Cr 121, eGFR 67, NT-proBNP 4298, normal hematology

What GDMT would you apply?

Phenotypes and Left Ventricular Ejection Fraction

LVEF < 40%	*HFrEF*
LVEF = 41-50%	*HFmrEF*
LVEF > 50%	*HFpEF*
Baseline LVEF ≤40%; ↑≥10 % points to LVEF >40% on the 2nd measurement	*HFimpEF*

Conventional vs. Contemporary Sequencing Strategies for the Initiation of Foundational Treatments of HFrEF

ACEIs/ARBs

↓

β-blockers

↓

MRAs

↓

Switch to ARNI

↓

$SGLT_2$ inhibitors

Individual titration, needs 6 months

Particularly in patients with low BP and borderline renal function

β-blockers, $SGLT_2$ inhibitors

↓

Switch to/Initiate ARNI

↓

MRAs

Ivabradine
Vericiguat

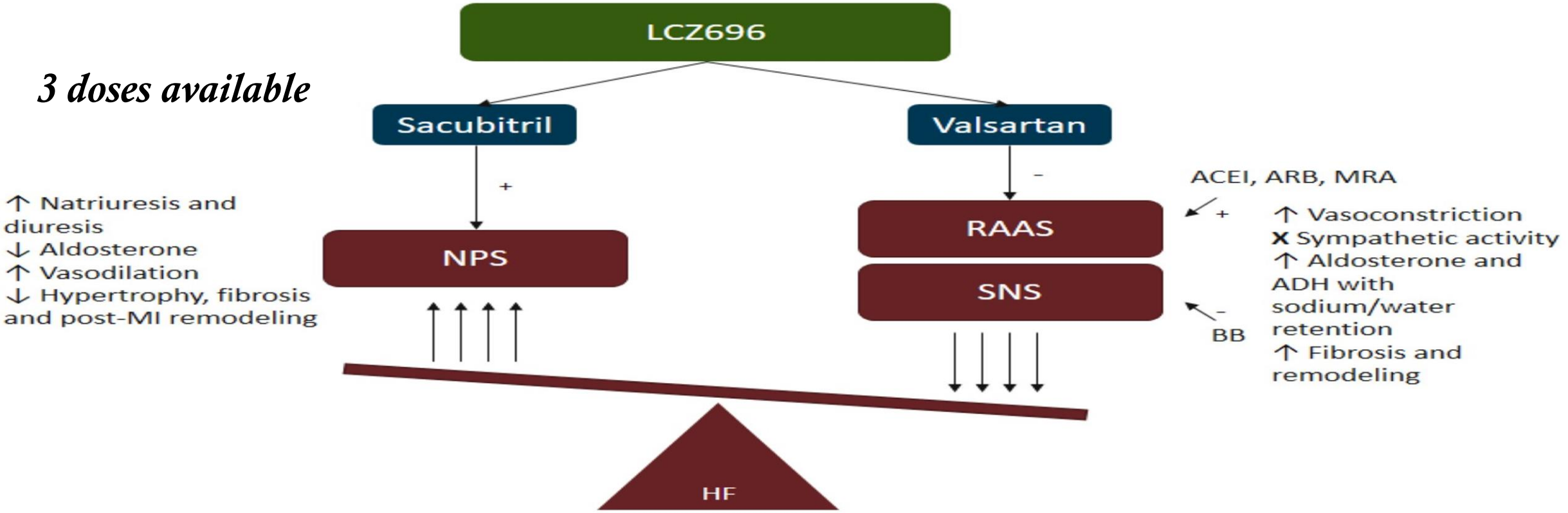
All steps completed in 4 weeks, dose titration later

Adapted from McMurray JV et al. Circ 2021

LCZ696 = Sacubitril/Valsartan = Entresto = An Angiotensin Receptor Neprilysin Inhibitor (ARNI)

Sacubitril/Valsartan, an ARNI, Mechanism of Action

3 doses available



Yandrapalli S, et al. *Ther Adv Cardiovasc Dis*. 2018;12:217-231.

The Evidence
ARNI in Chronic HFrEF: the PARADIGM-HF Trial

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

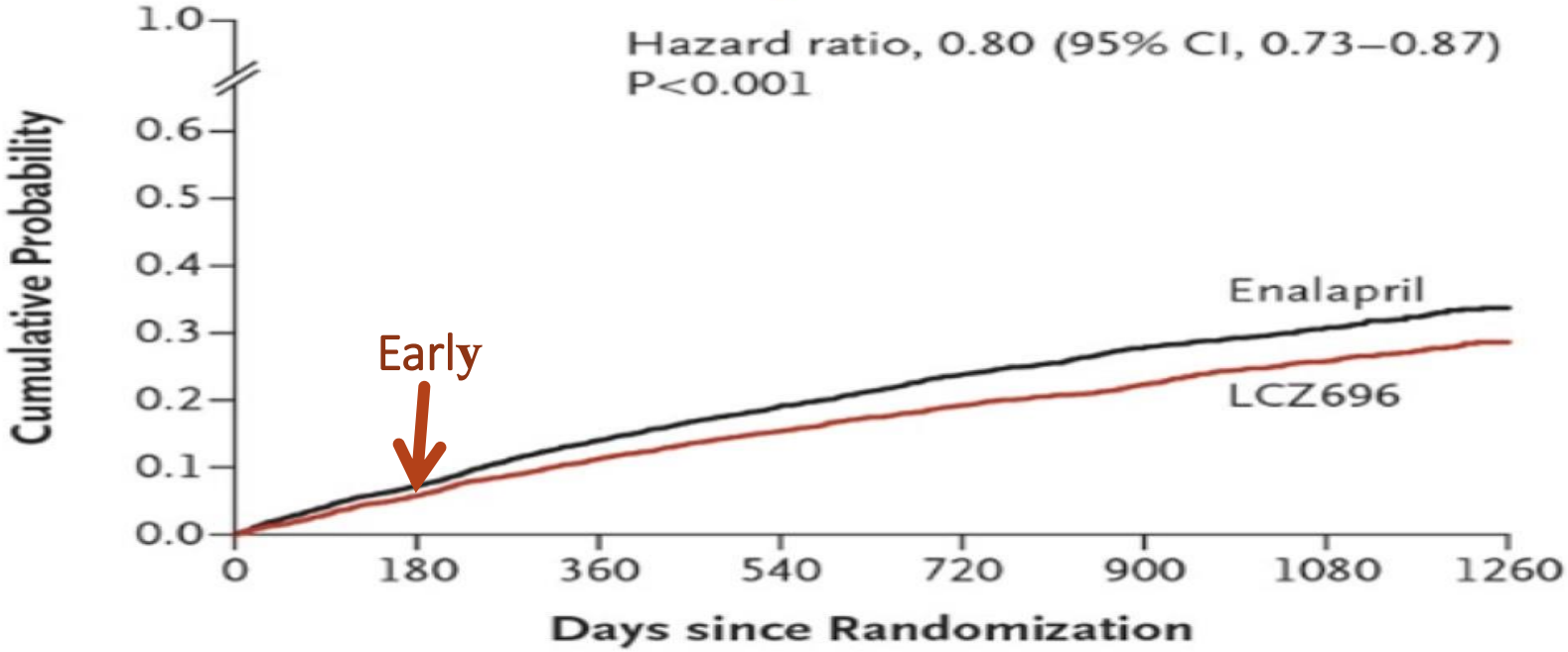
Milton Packer, John J.V. McMurray, Akshay S. Desai, Jianjian Gong, Marty P. Lefkowitz, Adel R. Rizkala, Jean L. Rouleau, Victor Shi, Scott D. Solomon, Karl Swedberg, Michael R. Zile, Karl Andersen, Juan Luis Arango, Malcolm Arnold, Jan Belohlavek, Michael Böhm, Sergey A. Boytsov, Lesley J. Burgess, Walter Cabrera, Carlos Calvo, Chen-Huan Chen, Andrej Dukat, Yan Carlos Duarte, Andrejs Erglis, Michael Fu, Efrain A. Gomez, Angel Gonzàlez-Medina, Albert A. Hagege, Jing Huang, Tzvetana M. Katova, Songsak Kiatchoosakun, Kee-Sik Kim, Ömer Kozan, Edmundo A. Bayram Llamas, Felipe Martinez, Bela Merkely, Ivan Mendoza, Arend Mosterd, Marta Negrusz-Kawecka, Keijo Peuhkurinen, Felix Ramires, Jens Refsgaard, Arvo Rosenthal, Michele Senni, Antonio S. Sibulo, José Silva Cardoso, Iain B. Squire, Randall C. Starling, John R. Teerlink, Johan Vanhaecke, Dragos Vinereanu and Raymond C. Wong

DOI: 10.1161/CIRCULATIONAHA.114.013748

ARNI as a Foundational Therapy in HFrEF: A Landmark Trial

Benefit of ARNI in HFrEF: Results of the PARADIGM-HF Trial

Composite of CV Death or First Hospitalization for Worsening HF*



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

*Primary endpoint.

McMurray JJV, et al. *N Eng J Med*. 2014;371:993-1004.

Initiation of Sacubitril/Valsartan in HF Patients before Hospital Discharge

ORIGINAL ARTICLE

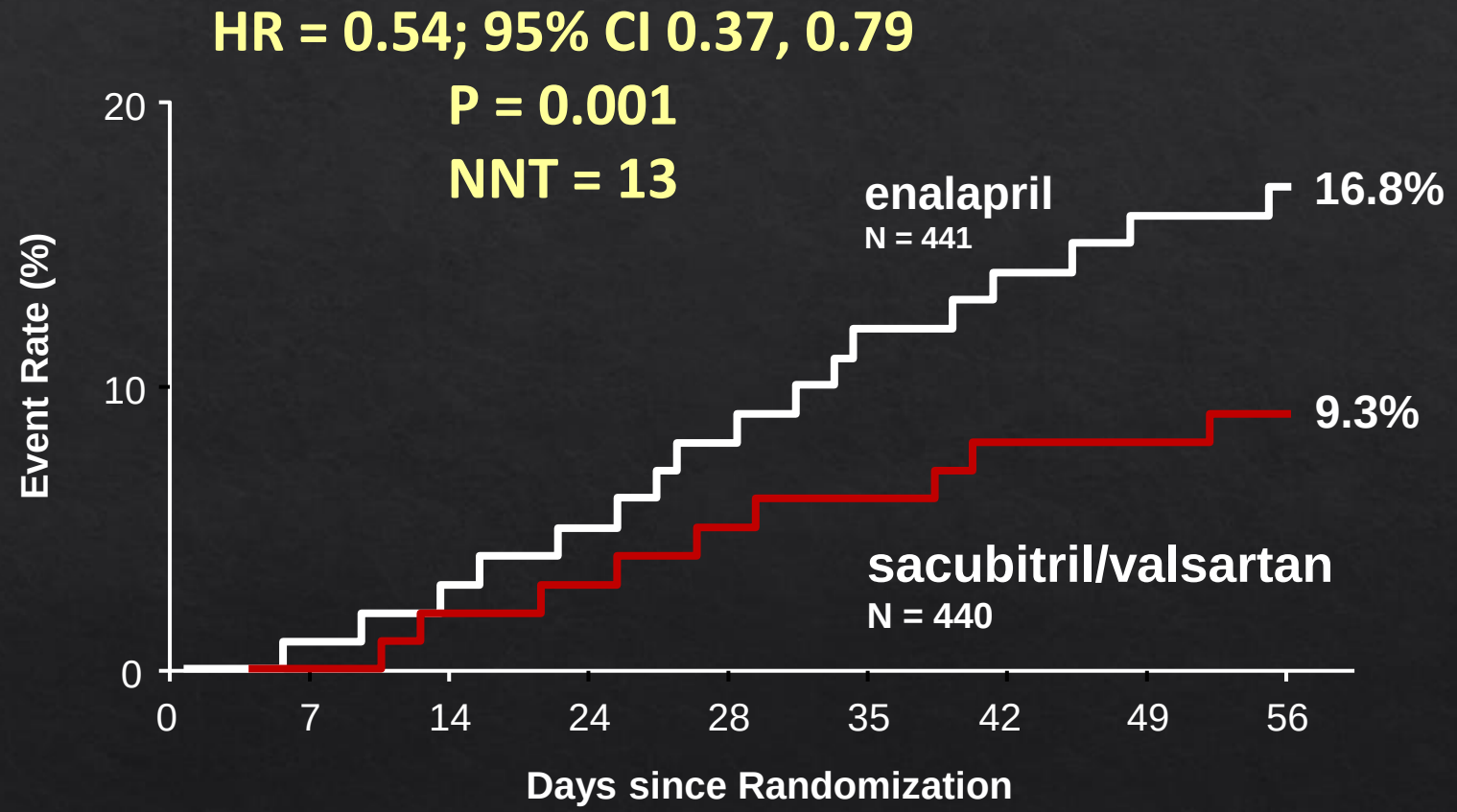
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

Velazquez EJ et al. N Engl J Med 2018;380:539-48

Serious Composite Clinical Endpoint:

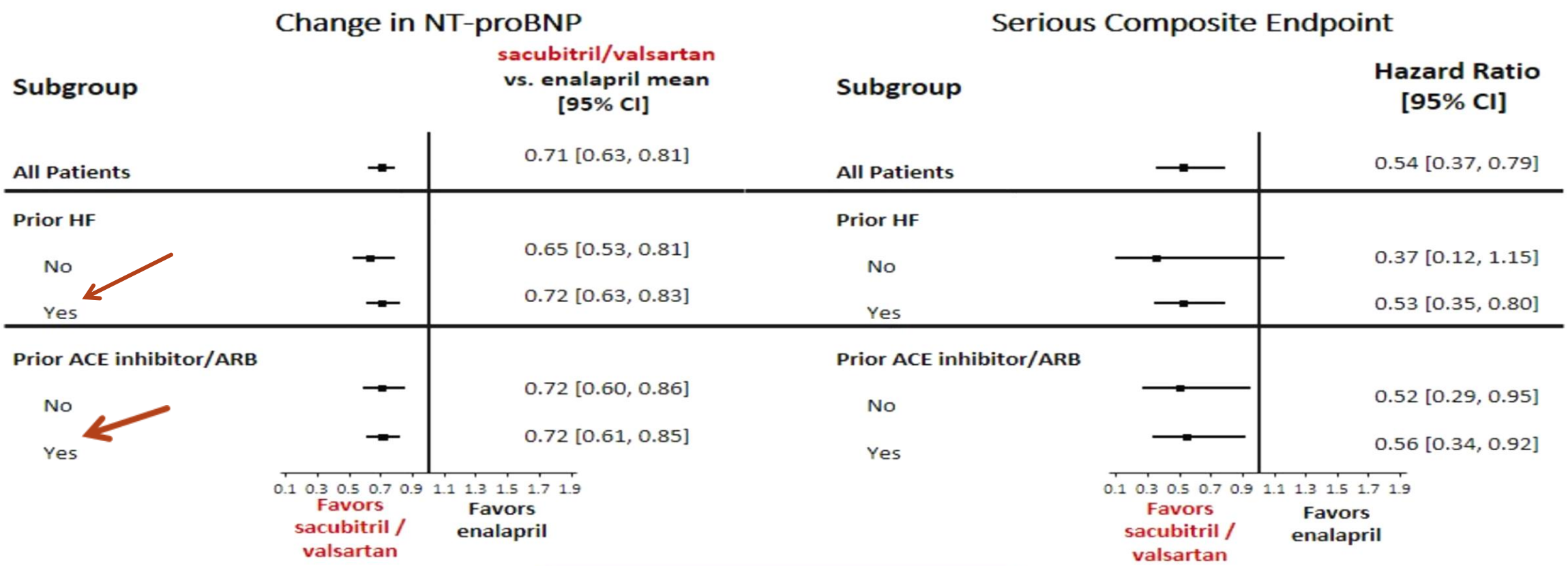
Death, HF re-hospitalization, LVAD, Transplant listing



Velazquez EJ et al. N Engl J Med 2018;380:539-48

Practice Changing!

PIONEER HF: Key Subgroup Analyses



P value (interaction) = NS

Velazquez EJ, et al. *N Engl J Med.* 2018;380:539-548.

CCS 2021 Heart Failure Guideline on ARNI

Recommendation - New

- **We recommend that patients admitted to hospital for acute decompensated HF with HFrEF should be switched to an ARNI, from an ACEi or ARB, once stabilized and prior to hospital discharge (Strong Recommendation; Moderate-Quality Evidence).**

Recommendation - New

- **We suggest that patients admitted to hospital with a new diagnosis of HFrEF should be started on an ARNI as first-line therapy, as an alternative to either an ACEi or ARB (Weak Recommendation; Moderate-Quality Evidence).**

McDonald M, et al. Can J Cardiol 2021;37:531-46

"New" Treatment for HFrEF: Vericiguat

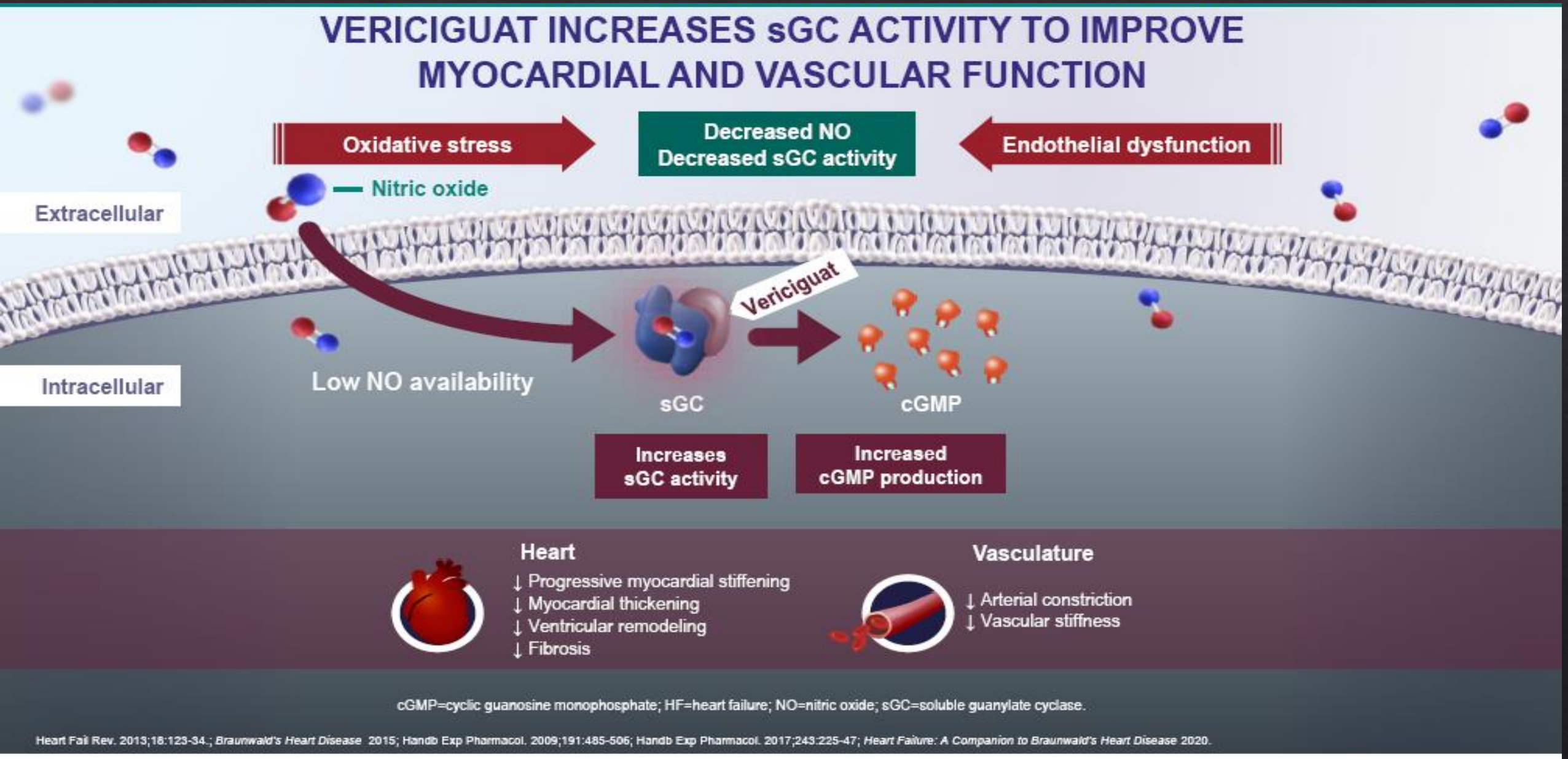
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2020 VOL. 382 NO. 20

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*

Vericiguat Mechanisms of Action



cGMP=cyclic guanosine monophosphate; HF=heart failure; NO=nitric oxide; sGC=soluble guanylate cyclase.

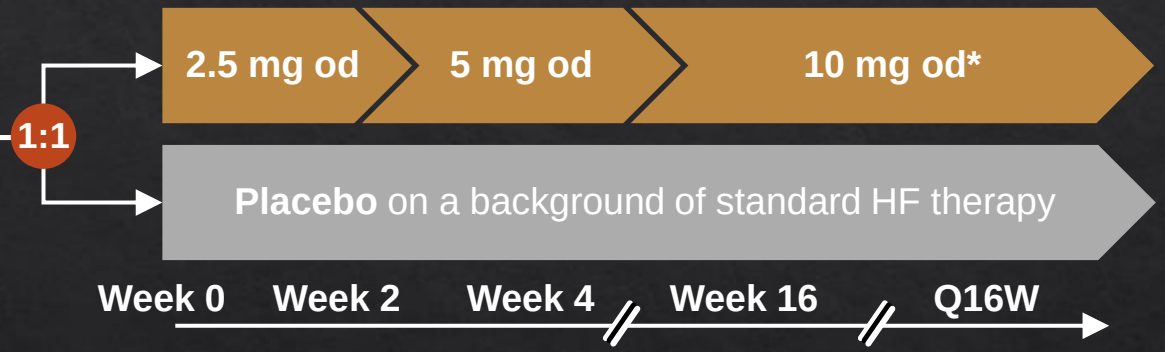
Heart Fail Rev. 2013;18:123-34.; *Braunwald's Heart Disease* 2015; Handb Exp Pharmacol. 2009;191:485-506; Handb Exp Pharmacol. 2017;243:225-47; *Heart Failure: A Companion to Braunwald's Heart Disease* 2020.

VICTORIA: Study Design[1,2]

A randomised, parallel-group, placebo-controlled, double-blind, event-driven, multicentre phase III trial

Eligibility criteria

- HFrEF (LVEF <45%)
- NYHA Class II–IV
- BNP: ≥300 pg/ml SR; ≥500 pg/ml + AF
- NT-proBNP: ≥1000 pg/ml SR; ≥1600 pg/ml + AF
- On guideline-directed medical therapy for HF
- eGFR: ≥15 ml/min/1.73 m^2 (15% cap: 15–30 ml/min/1.73 m^2)
- **HFH in 6 months** (20% cap: hospitalisation >3 months of randomisation) or outpatient IV diuretic treatment for HF within 3 months



Primary endpoint: Time to first occurrence of the composite of CV death or HFH (to ≅ 3.5 years)

Secondary endpoints (to ≅ 3.5 years):

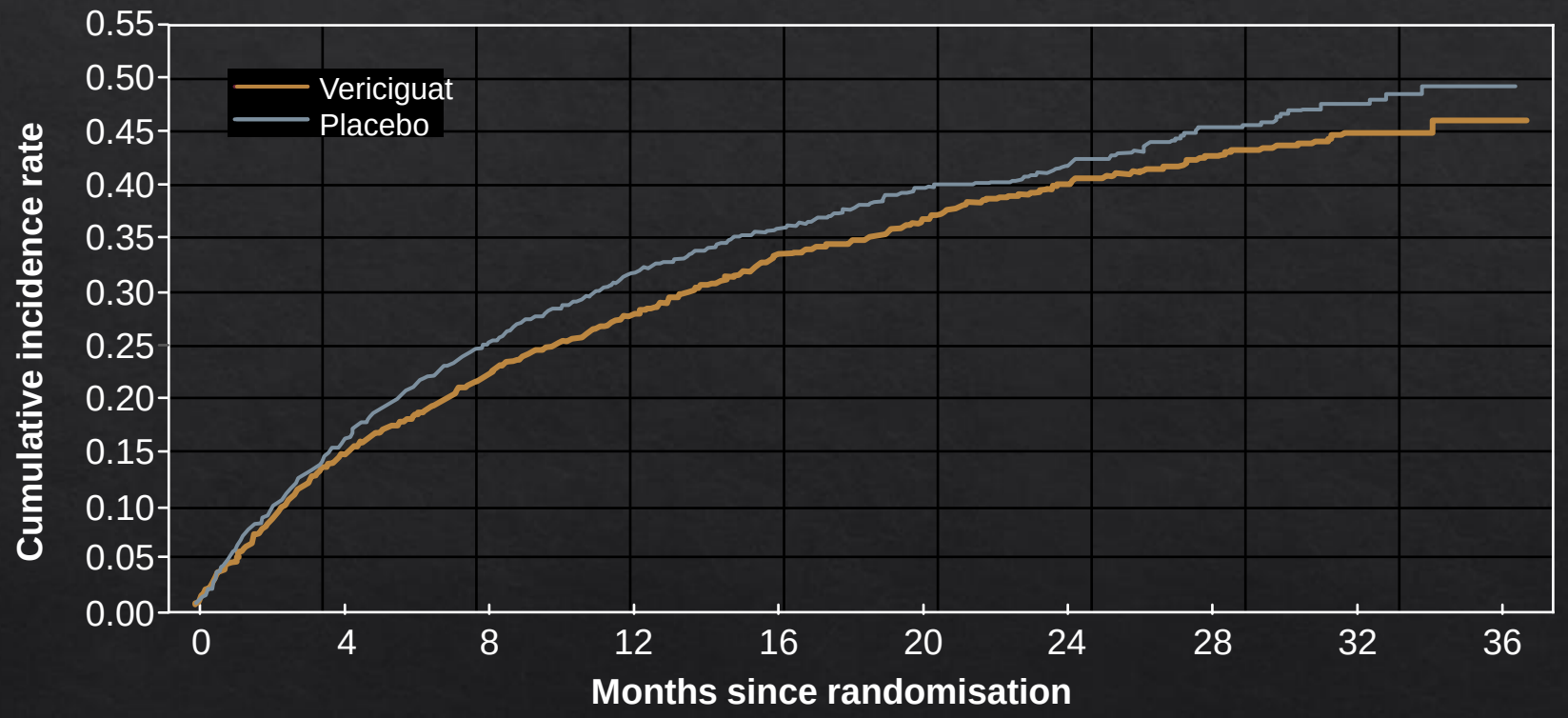
- Time to CV death
- Time to first HFH
- Time to first and subsequent HFHs
- Time to all-cause mortality
- Time to composite all-cause mortality or HFH

After approximately 12 months, 10 mg target dose achieved: vericiguat (89.2%); placebo (91.4%).

*If the 10 mg target dose was not reached, then up-titration was considered at subsequent study visits, based on protocol-specified criteria

1. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 2. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

VICTORIA Primary Outcome
CV Death and Time to First HF Hospitalization



Number of subjects at risk										
Vericiguat	2526	2099	1621	1154	826	577	348	125	1	0
Placebo	2524	2053	1555	1097	772	559	324	110	0	0

Median treatment: 10.8 months

Annual event rates for vericiguat and placebo per 100 patient-years were 33.6% and 37.8%, respectively

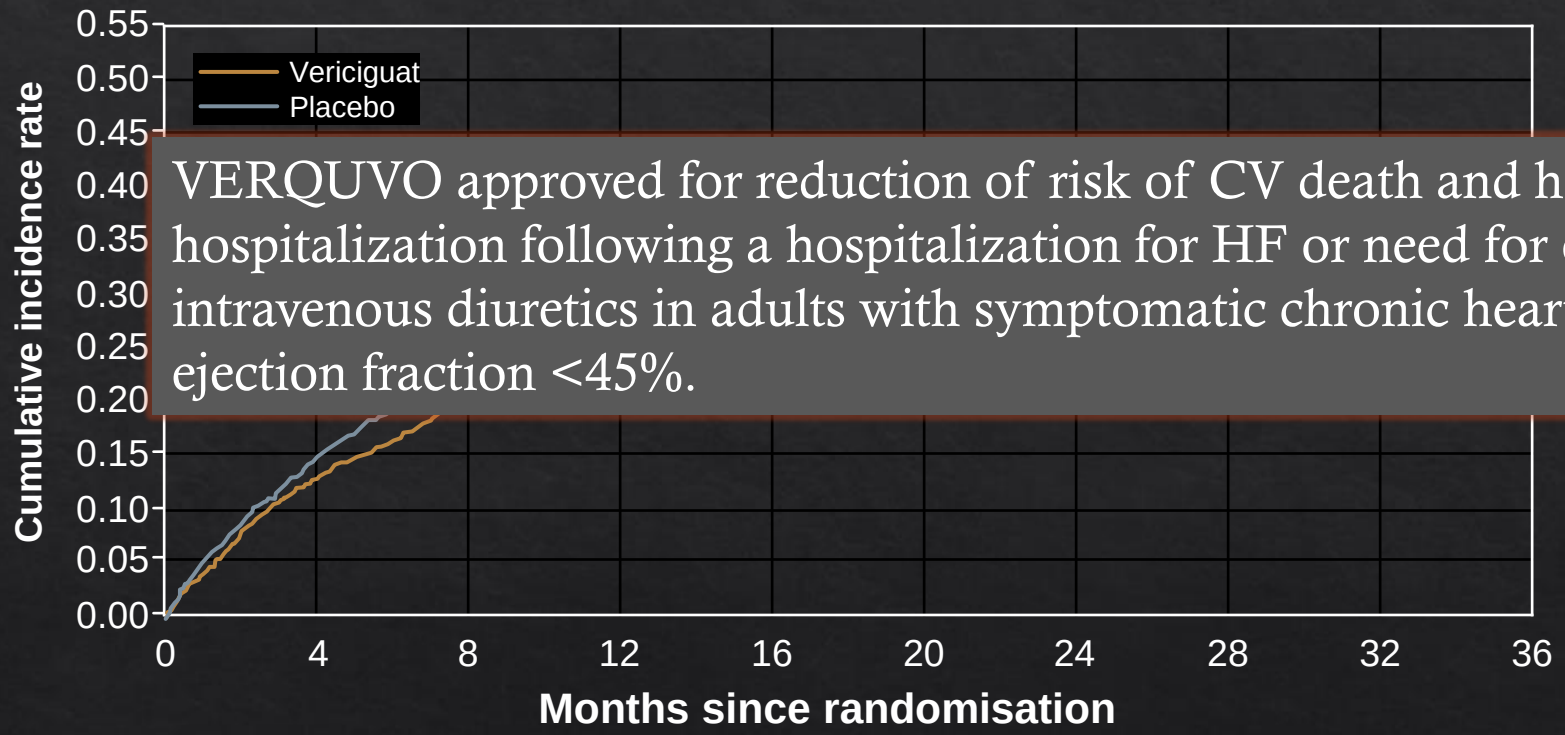
HR=0.90 (95% CI 0.82–0.98);
***p*=0.02**
ARR=4.2% per year
Annual NNT=24*

*Annual NNT = 100/4.2 = 24

Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

Heart Failure Hospitalization

Time to first heart failure hospitalization (HFH)



VERQUVO approved for reduction of risk of CV death and heart failure hospitalization following a hospitalization for HF or need for outpatient intravenous diuretics in adults with symptomatic chronic heart failure and ejection fraction <45%.

- Median treatment duration: 10.8 months
- …es for …acebo per 100 …e 25.9% and …ely

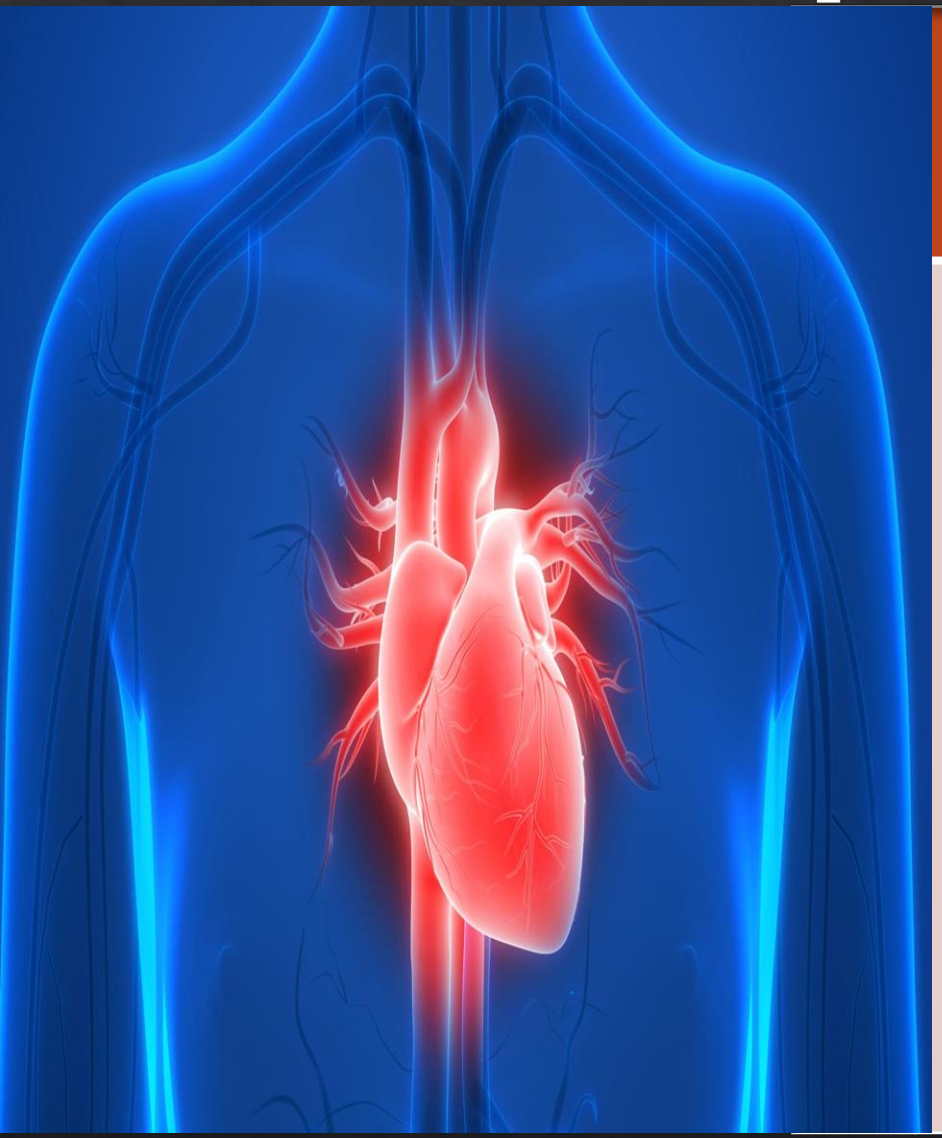
HR=0.90 (95% CI 0.81–1.00)
ARR=3.2% per year[2]
Annual NNT=31*

Number of subjects at risk										
Vericiguat	2526	2098	1620	1153	825	577	348	125	1	0
Placebo	2524	2052	1554	1096	771	558	323	110	0	0

*Calculations: annual NNT = 100/3.2 = 31

1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893; 2. Butler J et al. *Circulation.* 2020; doi: 10.1161/CIRCULATIONAHA.120.047086

Phenotypes and LVEF: Proposed New Classification

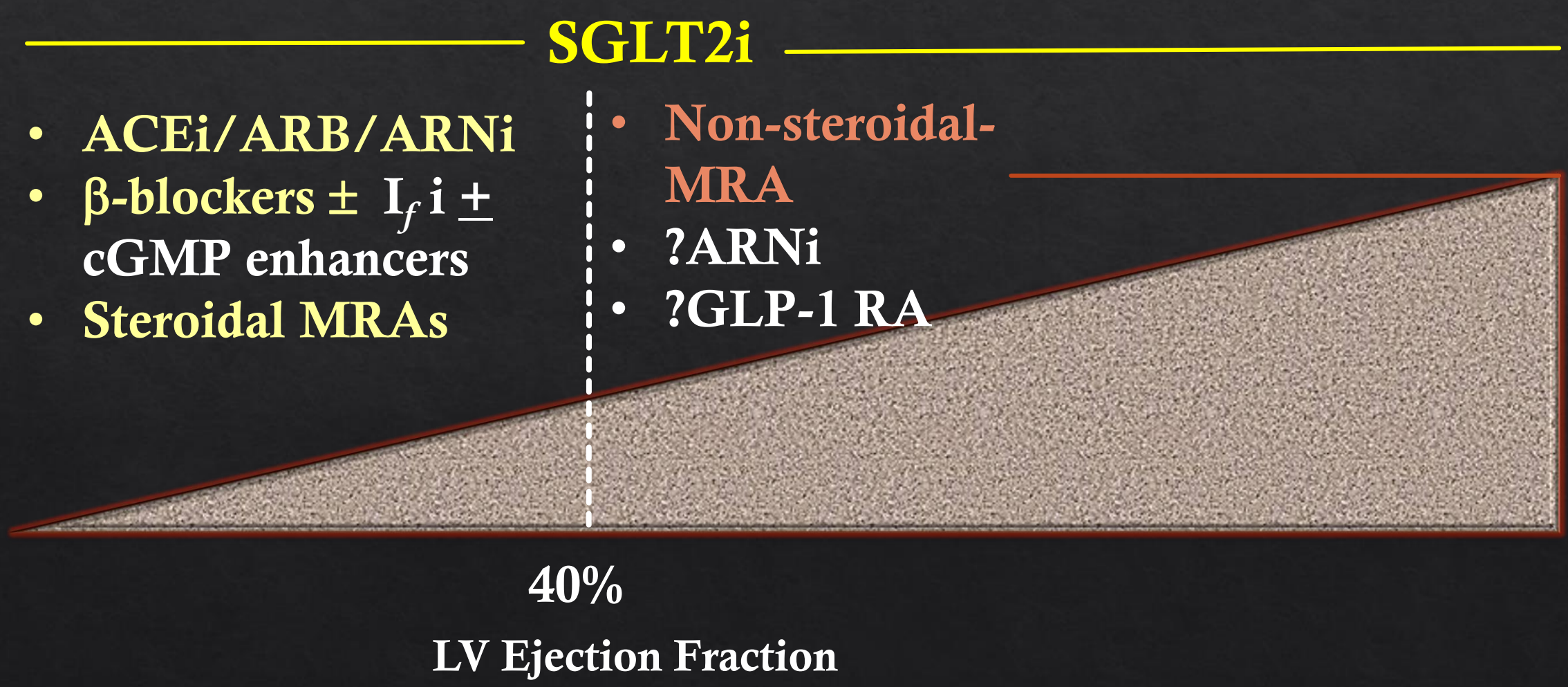


LVEF < 40%

LVEF≥ 40%

Foundational Therapy for Heart Failure

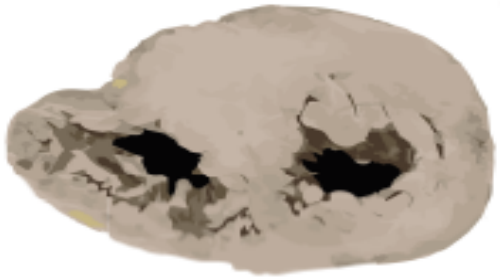
All Ejection Fractions 2025



OBJECTIVES

1. Discuss HFrEF: focused on specific topics with contemporary information
2. Review cardiomyopathy: focusing on the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) with new information

Epidemiology of transthyretin cardiac amyloidosis

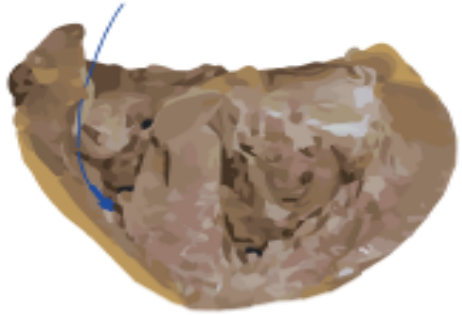


Hypertrophic cardiomyopathy
12.5% (95%CI:11.0-14.2)

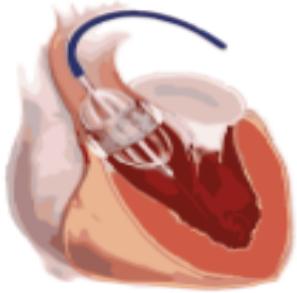
Heart failure
HFpEF/HFmrEF: 13.1% (95%CI:11.4-14.9)
HFrEF: 9.7% (95%CI:4.6-17.1)

Prevalence of ATTR-CM in frequent clinical scenarios

Incidental
Bone scintigraphy for non-CV reasons:
0.52% (95%CI: 0.46-0.58)



Conduction disorders
7.6% (95%CI:4.4-11.9)



Aortic stenosis
Aortic Stenosis: 8.2% (95%CI:7.1-9.4)
TAVI: 8.7% (95%CI:7.5-10.1)
Surgical: 3.1% (95%CI:1.2-6.9)

Diagnosis of Transthyretin amyloidosis

Maintain an index of suspicion

- Unexplained heart failure
- Unexplained LVH
- History of carpal tunnel syndrome
- History of spinal stenosis

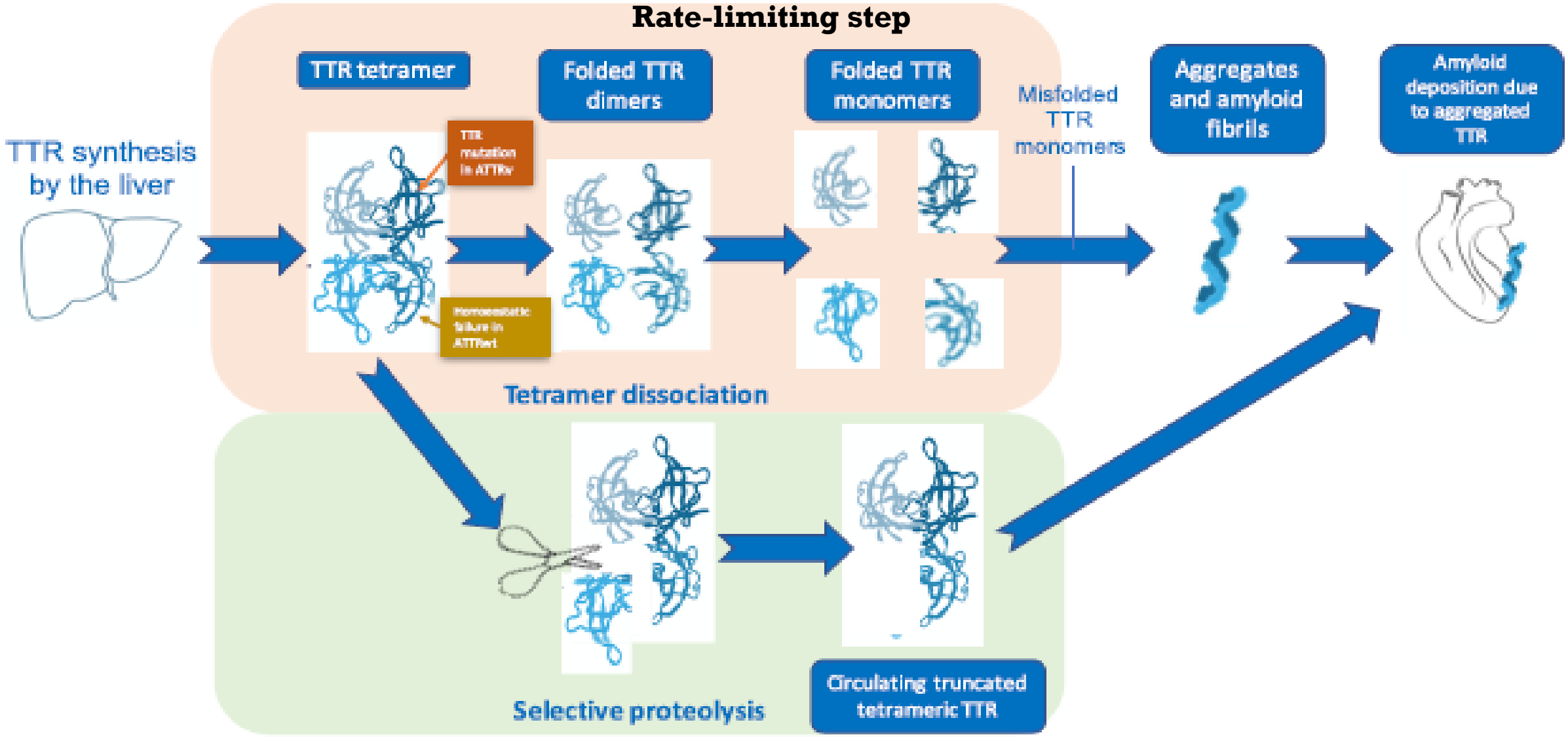
Diagnostic tests

- ECG, Echocardiogram
- Cardiac MRI
- PET scan
- Endomyocardial biopsy

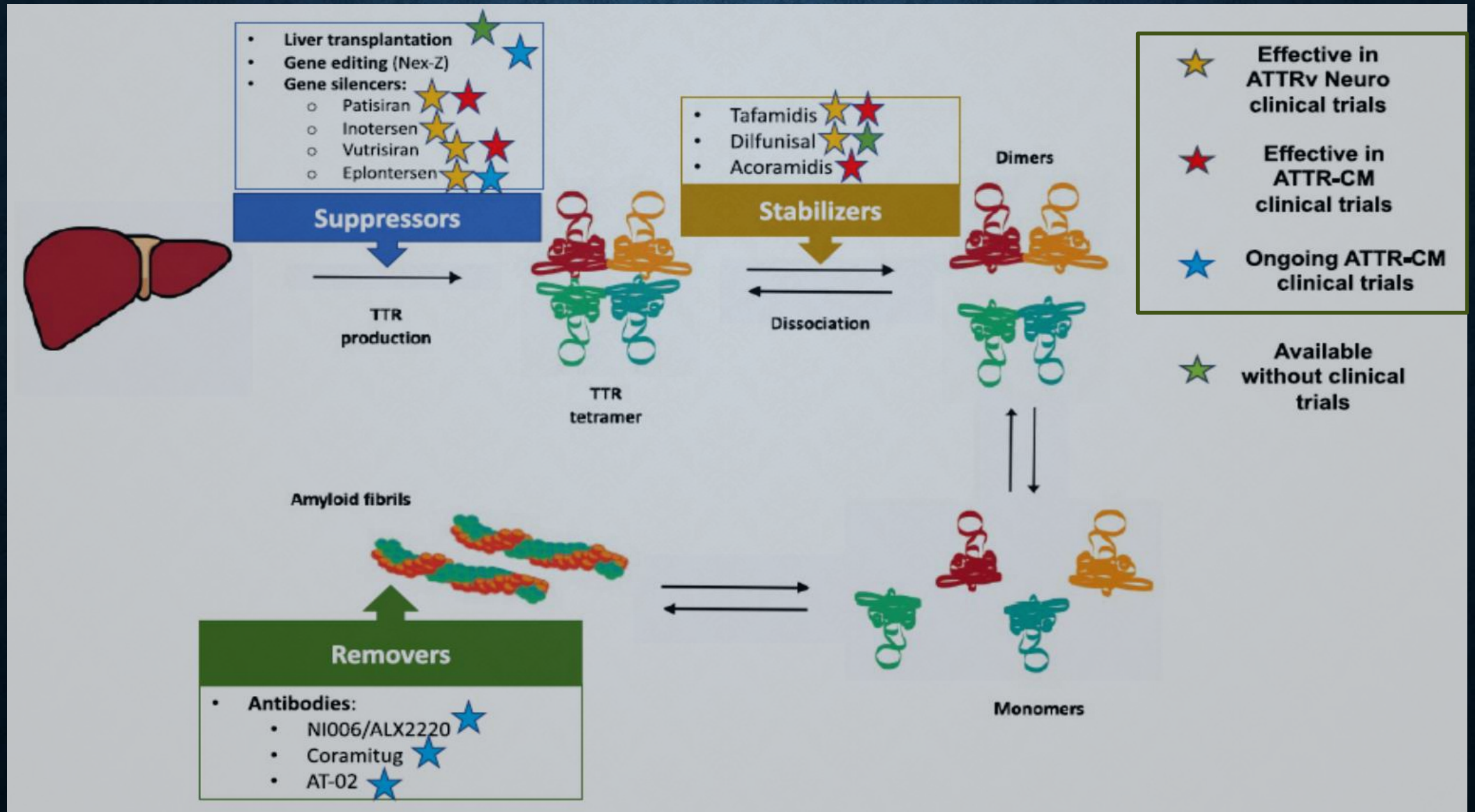
Common Types of Amyloidosis with Cardiac Involvement

Transthyretin Cardiomyopathy, Wild Type (ATTRwt-CM)	Cardiomyopathy
Transthyretin Cardiomyopathy, Hereditary/Variant Type (ATTRv-CM)	Cardiomyopathy Peripheral neuropathy Autonomic neuropathy
Light Chain Amyloidosis Cardiomyopathy (AL-CM)	Multiorgan involvement

Transthyretin Amyloidogenic Cascade



Transthyretin amyloidosis-specific therapies



Gene silencers

- Inotersin
- Eplontersen

2'-O- antisense oligonucleotide

- Patisiran*
- **Vultrisirin***

RNA interference (RNAi)

- All approved for treatment of neuropathy
- *Amvuttra®, FDA approved for treatment of cardiomyopathy

THE HELIOS-B TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

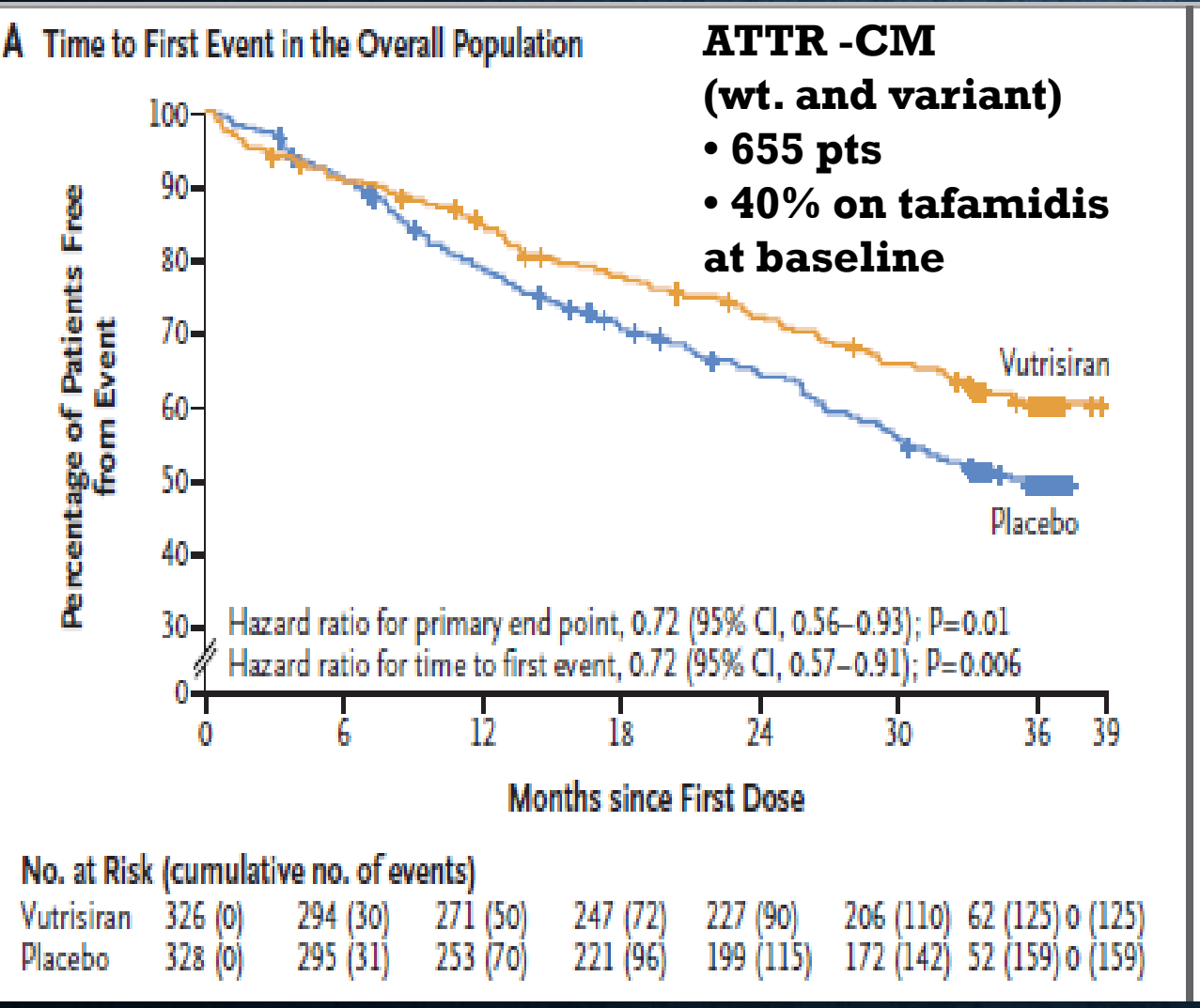
Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

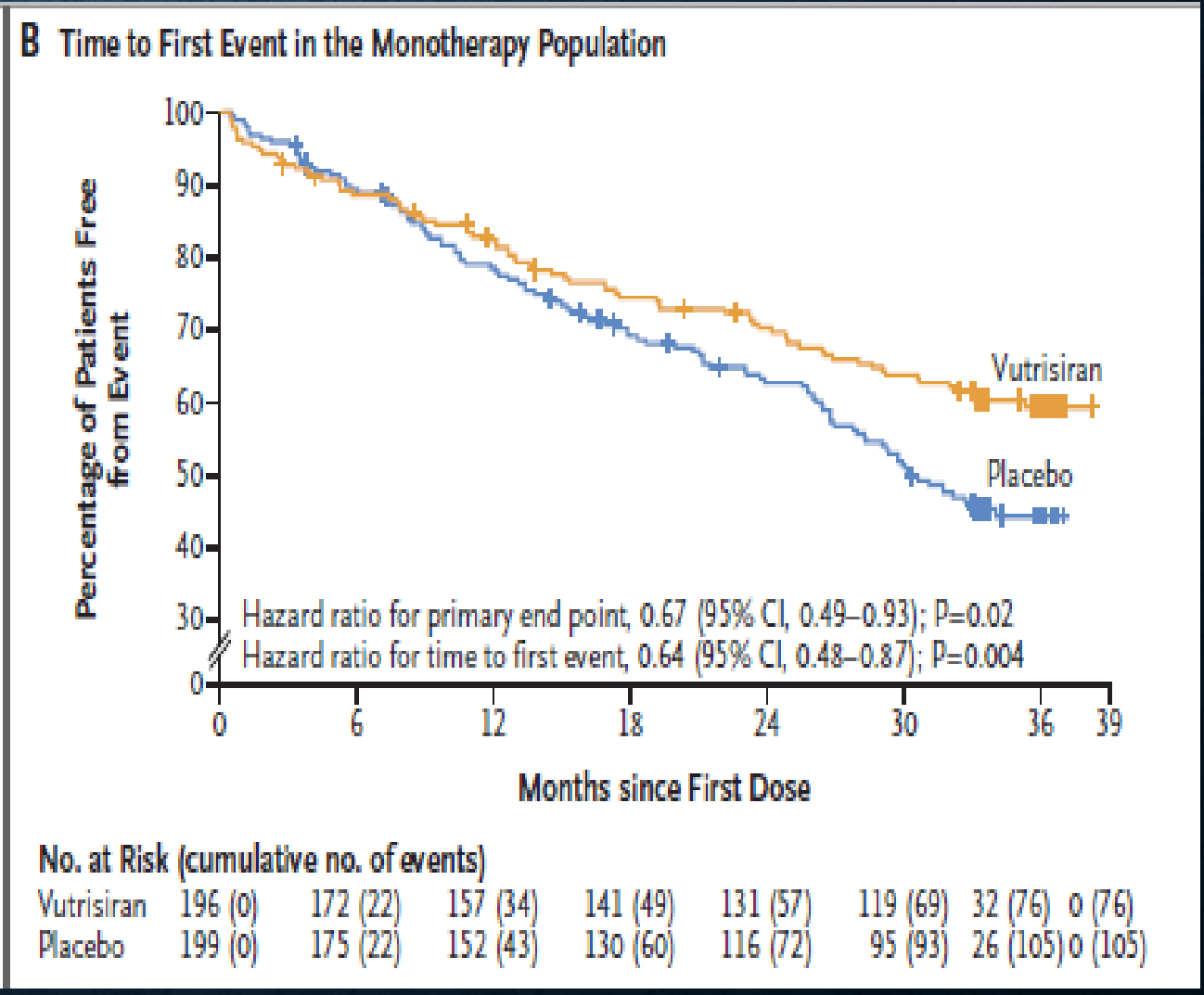
M. Fontana, J.L. Berk, J.D. Gillmore, R.M. Witteles, M. Grogan, B. Drachman, T. Damy, P. Garcia-Pavia, J. Taubel, S.D. Solomon, F.H. Sheikh, N. Tahara, J. González-Costello, K. Tsujita, C. Morbach, Z. Pozsonyi, M.C. Petrie, D. Delgado, P. Van der Meer, A. Jabbour, A. Bondue, D. Kim, O. Azevedo, S. Hvitfeldt Poulsen, A. Yilmaz, E.A. Jankowska, V. Algalarrondo, A. Slugg, P.P. Garg, K.L. Boyle, E. Yureneva, N. Silliman, L. Yang, J. Chen, S.A. Eraly, J. Vest, and M.S. Maurer, for the HELIOS-B Trial Investigators*

655 patients testing an RNA interference therapeutic agent

HELIOS-B: PRIMARY ENDPOINT

ATTR -CM (wt. and variant)
- **655 pts**
- **40% on tafamidis at baseline**





TTR STABILIZERS

- Tafamidis*
- Acoramidis**

*Demonstrated both neurological and cardiac effects and Health Canada and FDA approved

**FDA approved (Attruby®)

ANOTHER STABILIZER: ACORAMIDIS*

ORIGINAL ARTICLE

Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

J.D. Gillmore, D.P. Judge, F. Cappelli, M. Fontana, P. Garcia-Pavia, S. Gibbs, M. Grogan, M. Hanna, J. Hoffman, A. Masri, M.S. Maurer, J. Nativi-Nicolau, L. Obici, S.H. Poulsen, F. Rockhold, K.B. Shah, P. Soman, J. Garg, K. Chiswell, H. Xu, X. Cao, T. Lystig, U. Sinha, and J.C. Fox, for the ATTRibute-CM Investigators*

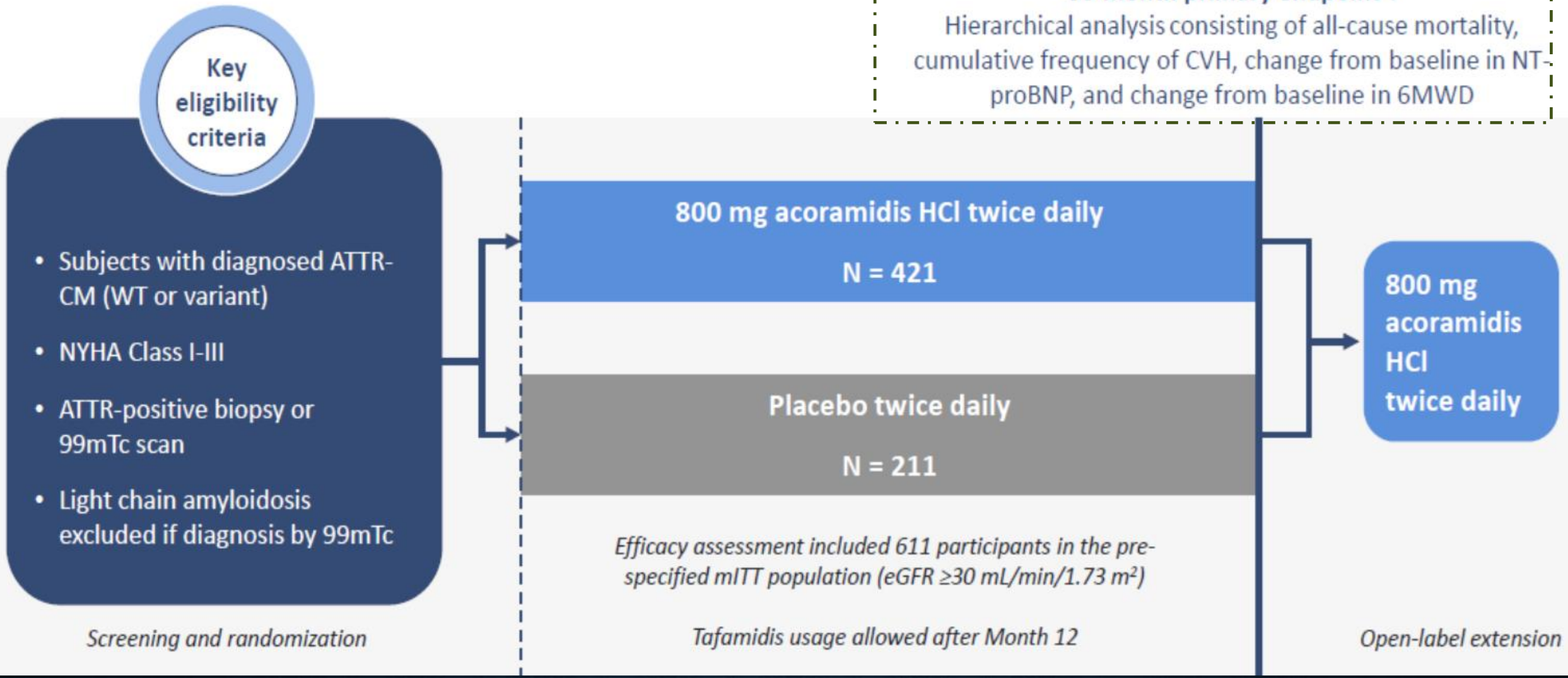
Acoramidis (AG-10)* is a high-affinity TTR stabilizer that inhibits dissociation of tetrameric TTR resulting in >90% stabilization

** Attruby®, FDA approved, not yet approved by Health Canada*

Gilmore, JD , et al. N Engl J Med 2024;390:132-42

ATTRibute-CM study design[1,2]

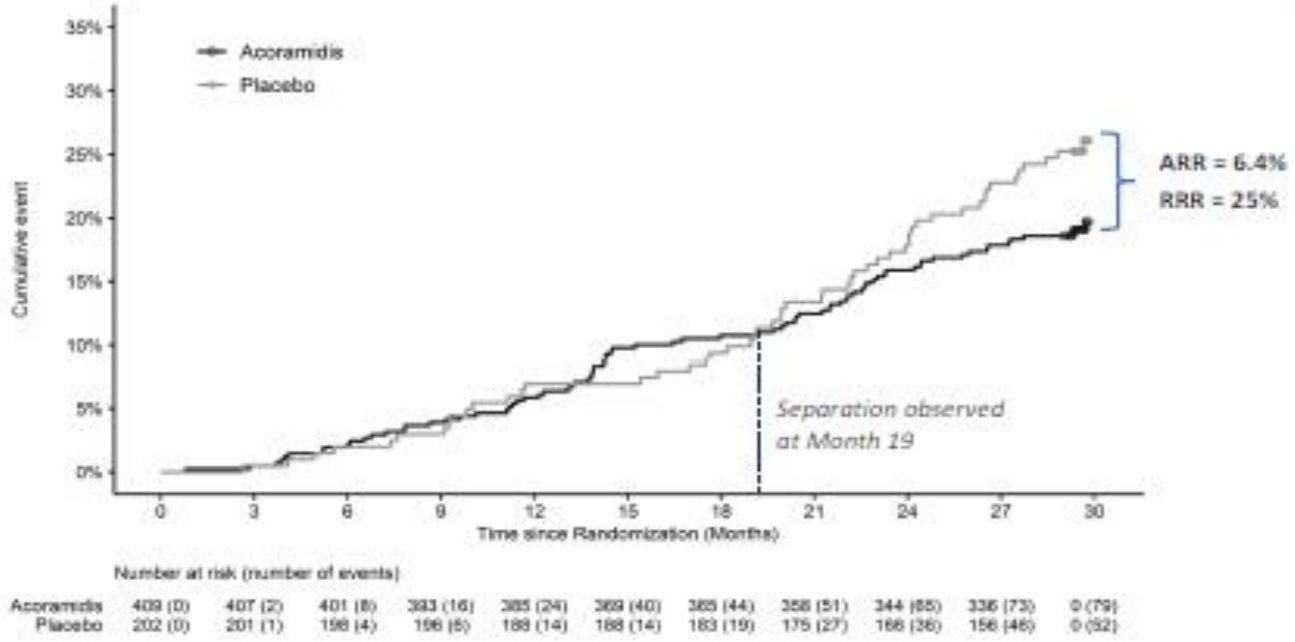
30-month primary endpoint[3]:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD

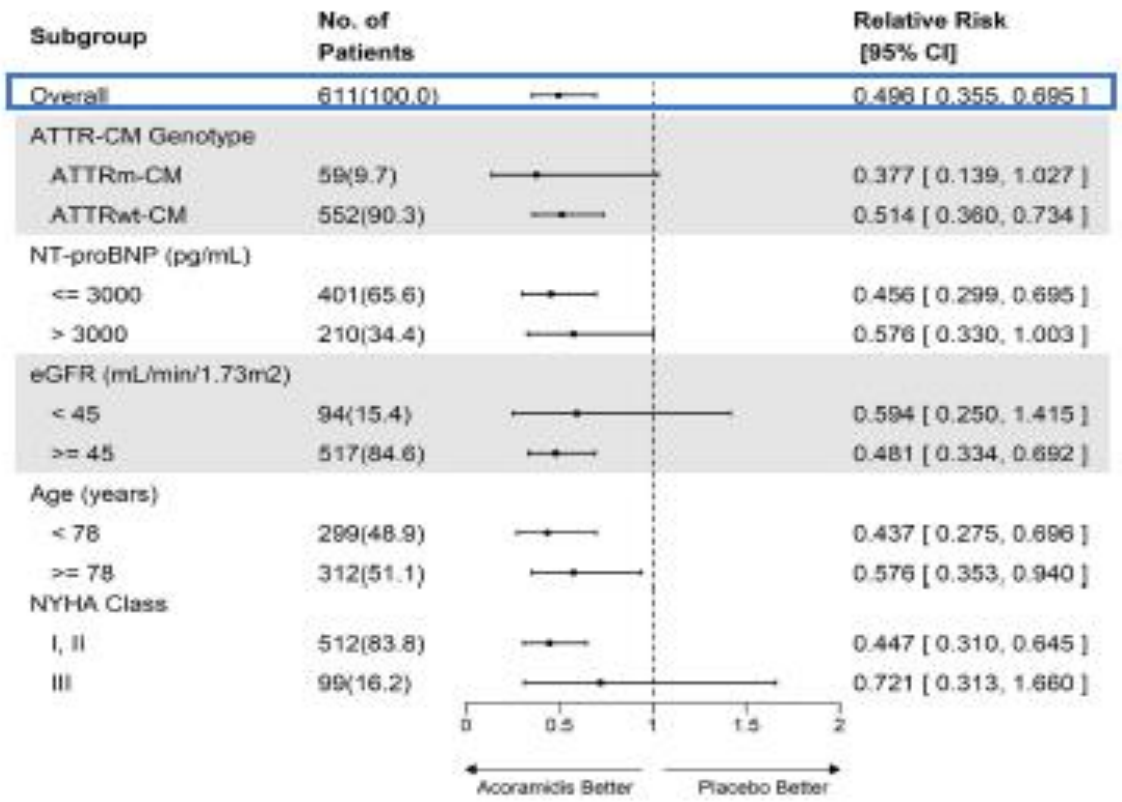


Gilmore, JD , et al. N Engl J Med 2024;390:132-42

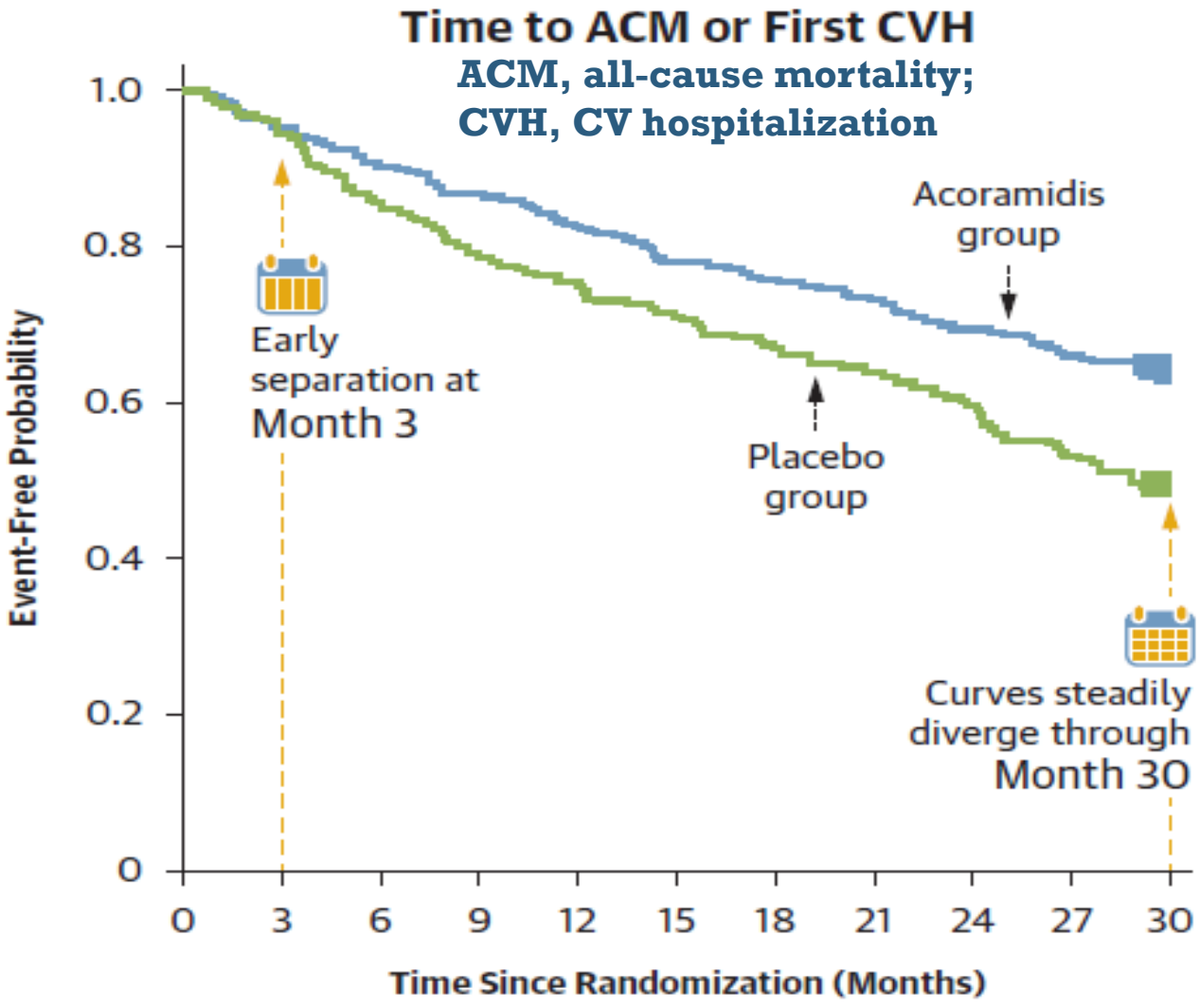
ATTRibute-CM Trial: Acoramidis

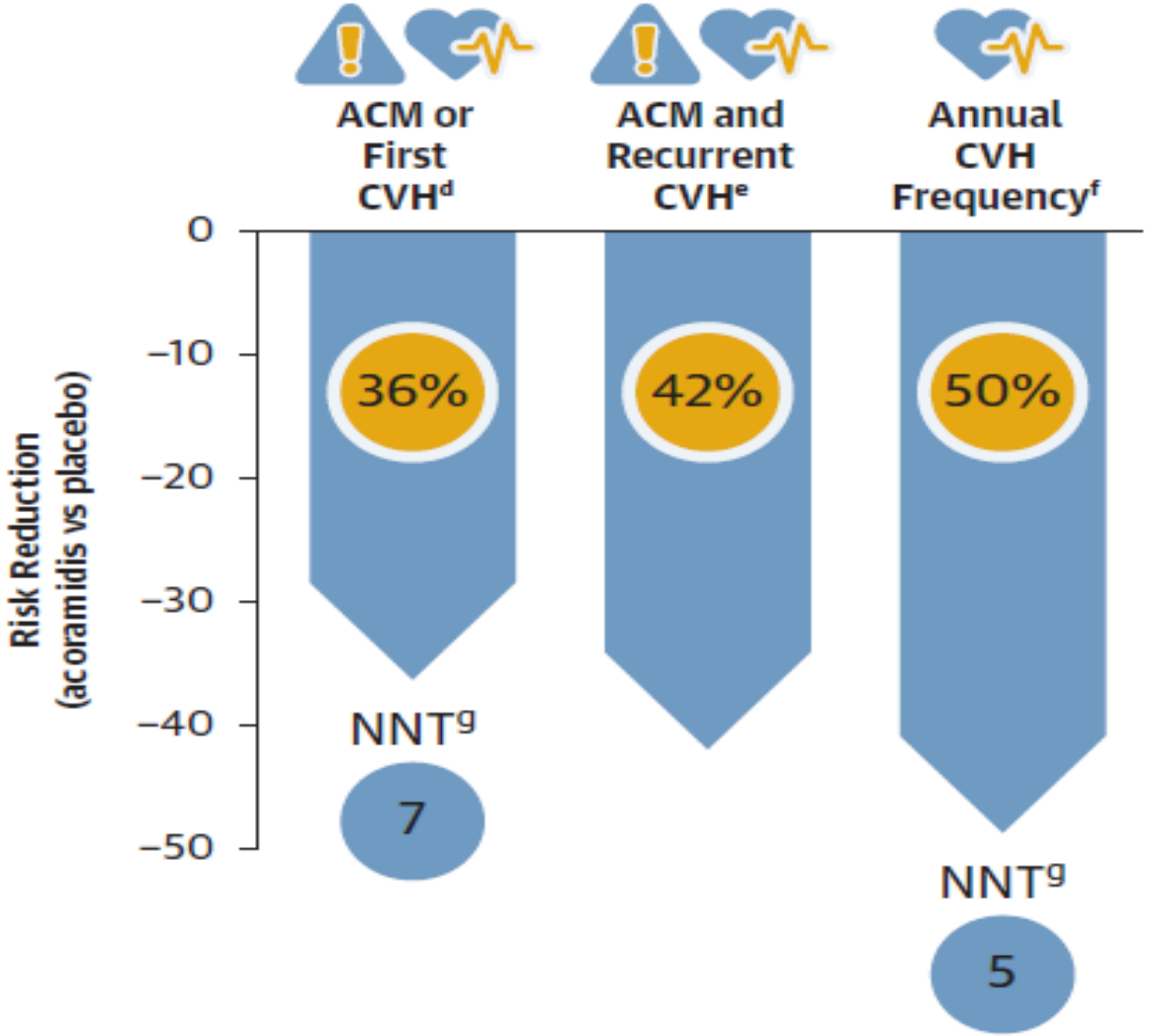
- Met primary composite endpoint (mortality, CVH, 6-MWT, KCCQ; $p<0.0001$)
- 50% RRR in CV hospitalization





New data: Early Benefits of Acoramidis on All-Cause Mortality and CV-Related Hospitalization in ATTR-CM





Judge DP, et al. JACC. 2025;85(10):1003–1014.

TRANSTHYRETIN AMYLOIDOSIS-SPECIFIC THERAPIES
APRIL 2025

Amyloidosis Types	ATTRwt	ATTRv	AL Amyloidosis
Cardiomyopathy	**Tafamidis, Acoramidis* Vultrisirin****	**Tafamidis Acoramidis***	Refer to hematology
Polyneuropathy	**Vultrisirin**	**Vultrisirin**	

* Attruby, not yet approved in Canada, but approved by FDA

** Amvuttra, FDA-approved for treatment of cardiomyopathy

ST. MICHAEL'S
UNITY HEALTH TORONTO

Cardiology for the Practitioner
Saturday, April 12, 2025
VIRTUAL

EVIDENCE AND GUIDELINE-RECOMMENDED MANAGEMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION AND CARDIOMYOPATHY

Conclusions

- Patient with HFrEF should received at least four agents as foundational therapy.
- The speed and sequence of initiation should be individualized, considering blood pressure and renal function
- Patients with ATTR cardiomyopathy should in general be first offered a stabilizer
- A silencer such as Vultrisirin can be considered in patients with intolerant to stabilizers or with mixed phenotypes